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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/250,056	02/12/99	MARKS J	2307E-852

EXAMINER	
HELMS, J	
ART UNIT	**PAPER NUMBER**
1642	15

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HM22/0710

DATE MAILED: 07/10/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/250,056	Marks et al
Examiner	**Group Art Unit**
Larry R. Helms Ph.D.	1642

☒ Responsive to communication(s) filed on *12 May 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1, 3-22, 34-44, 53, and 54* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3-22, 34-44, 53, and 54* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 2, 23-33, and 45-52 are canceled.

Claims 1, 3-22, 34-44, 53, and 54 are pending.

Claims 1, 4, 12-17, 21-22, 39, 43-44, ans 53-54 have been amended.

2. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

3. The following office action contains some NEW GROUNDS of rejections.

Rejections withdrawn

4. The rejection of claims under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

5. The rejection of claims under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is withdrawn in view of the amendments to the claims.

6. The rejection of claims 1, 3, 14-15, and 21-22 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendment to the claims.

7. The rejection of claims under 35 U.S.C. 102(b) as being anticipated by Maier et al (Cancer Research, 51:5361-5369, 1991) is withdrawn in view of the amendment to the claims and the new grounds of rejection.

Response to Arguments

Oath/Declaration

8. The oath or declaration is still defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is still defective because:

It does not state that the person making the oath or declaration has reviewed and understands the contents of the specification, including the claims, **as amended by any amendment** [emphasis added] specifically referred to in the oath or declaration.

Information Disclosure Statement

9. The references C40, B6, B7, and B8 were crossed through because it is not clear that international search reports are publicly available. The response states that international search reports are published and generally available. This may be correct but it is still unclear if applicants want the entire reference, including those references cited in the international report, considered. If all references are to be considered then the references should be submitted on a

separate form 1449 and supplied to the Examiner for consideration. Accordingly, C40, B6, B7, and B8 will not appear on the face of the patent, should this application go on to issue. If applicant wishes to have the PCT applications cited in C40, B6, B7, and B8 to be considered and listed on the face of the patent, an IDS citing the PCT's under Foreign Patent Documents may be filed.

Specification

10. The specification is objected to again because of the following reasons:

a. The specification recites copending application USSN 08/665,202, for example, on page 31. The present status of all copending applications must be updated. This application is now U. S. Patent 5,977,322. The specification should be checked for all copending applications.

b. The specification still contains numerous errors, for example, on page 13, lines 26 and 27 the terms "2 :M" and "1 :M" appear. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

11. The rejection of claims 4-13, 16-20, 34-44, and 53-54, under 35 U.S.C. 112, first paragraph, is maintained and made again.

b. The claims have been amended, but still broadly encompass internalizing antibodies that specifically binds to a c-erbB2 receptor wherein said antibodies are selected from antibodies

having 70% sequence identity with SEQ ID NO:1 or SEQ ID NO:2 wherein the antibody has a binding affinity for c-erbB2 on cells of at least 10 mM and an antibody with less than a full complement of CDRs as recited in claims 6-13, 19-20, and claims 41-42. Claim 16 still broadly encompasses production of an anti-idiotypic antibody produced by presenting an antigen of an antibody that specifically binds c-erbB2 receptor comprising at least 10 contiguous amino acids in SEQ ID NO:1 or SEQ ID NO:2. The claim still broadly encompasses 10 residues anywhere in the antibody.

c. The response on pages 9-13 has been carefully considered but has been deemed to be not persuasive. The response states that "The examiner is reminded that to be enabling under 112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention." and that some experimentation is necessary does not constitute lack of enablement (See page 10). The statement is correct that enablement encompasses making and using the claimed invention. The rejection under 112, first paragraph was made due to a lack of enablement provided by the specification, specifically it is known in the art how to make (1) substitutions within an antibody sequence, (2) calculate 70% identity of one sequence to another, and (3) produce a protein that contains one or two CDRs, however, applicant has not demonstrated how to use such proteins. It is unclear that an antibody that contains one, two, or three CDR would bind antigen as claimed. In addition, the specification does not enable the myriad of antibodies encompasses by claim 4 which recites an antibody that is 70% sequence identity with SEQ ID NO:1 or 2 that would bind to the c-erbB2 on cells at 10

mM. At this concentration there would be significant cross reactivity with many antibodies and these antibodies would not function as claimed in claim 1. Moreover, it is not clear if an antibody that comprises at least 10 contiguous amino acids (which can be framework residues) from the polypeptide as set forth in SEQ ID NO:1 or 2 would bind specifically to the c-erbB2 receptor as claimed in claim 16. As stated in the rejection in the previous Office Action the art of record demonstrates it is unpredictable how to use the claimed antibodies as broadly claimed. The response set forth on pages 9-13 does not address the unpredictability in the art as evidenced by Rudikoff et al, Panka et al, Adair et al, and Amit et al. In response to the Doctrine of equivalents at page 13, applicants have amended claim 1 to recite a single chain antibody, however, applicants have changed the scope of the claim by reciting "that is cross reactive with F5 (SEQ ID NO:1) or C1 (SEQ ID NO:2)".

The following contains some new grounds of rejections.

Claim Rejections - 35 USC § 112

12. Claims 1, 3-22, 34-44, and 53-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 and those depending on claim 1 are indefinite for reciting "that is cross reactive with F5 (SEQ ID NO:1) or C1 (SEQ ID NO:2) at c-erbB2" for the exact meaning of the

phrase is not clear. It is not clear if the single chain antibody is cross reactive with the antibodies F5 or C1 or the single chain antibody specifically binds to the same epitope defined by F5 or C1? Amending the claim to recite a singlechain antibody that specifically binds a c-erbB2 receptor, wherein said antibody binds to the epitope defined by F5 (SEQ ID NO:1) or C1 (SEQ ID NO:2) would be sufficient to obviate this part of the rejection.

b. Claim 16 and those depending on claim 16 is indefinite for reciting "does not bind to antisera raised..... and in SEQ ID NO:2." for the exact meaning of the phrase is not clear. The claim is drawn to a single chain antibody which (1) is used to elicit an immune response for production of an anti-idiotypic antibody that binds to SEQ ID NO:1 or SEQ ID NO:2, however, it is not clear if the antibody is not intended to bind to an antibody or antisera raised against SEQ ID NO:1 and 2 and it is not clear what antibody has been immunosorbed.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1, 34-38, and 53-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maier et al (Cancer Res. 51:5361-5369, 1991) and further in view of Bird et al (Science 242:423-426, 1988).

a. Briefly the claims are drawn to a single chain antibody that specifically binds to a c-erbB2 receptor that is cross reactive with F5 or C1 and is an internalizing antibody. Further, the antibody has an effector molecule which is a radionuclide and the antibody binds to the receptor on breast cancer cells.

c. Maier et al teach the monoclonal antibody, TA1, which is an internalizing antibody which specifically binds to the c-erbB2 receptor (see abstract). Maier et al also teach the radiolabelling of the TA1 antibody (see p 5362, radiolabelling of antibodies) as well as immunotoxins (page 5362, Antibodies and Immunotoxins), and gold sols (see page 5362) and the specific binding of the gold sol labeled TA1 to SKBr3 breast cancer cells (see p 5363, 1st paragraph). Maier et al also teach the TA1 antibody in PBS (page 5362, Flow Cytometry). Maier et al does not teach a single chain antibody. This deficiency is made up for in the teachings of Bird et al.

d. Bird et al teach a single chain antibody (see entire document).

e. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody of Maier et al and produce a single chain antibody as taught by Bird et al.

f. One of ordinary skill in the art would have been motivated to have used the antibody of Maier et al and produce a single chain antibody as taught by Bird et al because Bird et al teach "Single-chain antigen binding proteins are expected to have advantages in clinical applications because of their small size." (see page 426). In addition, one of ordinary skill in the art would have been motivated to have used the antibody of Maier et al and produce a single chain antibody as taught by Bird et al because the c-erbB2 would likely "be an effective target for an immunotoxin" (see page 5361). Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in using the antibody of Maier et al and produce a single chain antibody as taught by Bird et al because Bird et al teach "These proteins have the same specificities and affinities for their antigens as the monoclonal antibodies whose VL and VH sequences were used to construct the recombinant genes" (see abstract).

g. Because Maier et al is silent as to whether the antibody is cross reactive with F5 or C1, it is the Examiner's position that Maier et al have produced an antibody that has the same properties as recited in the claims and that this antibody has the same properties as that claimed in that binds to a c-erbB2 receptor and that it is internalizing. One of ordinary skill in the art would reasonably conclude that Maier et al's antibody also possesses the same properties and, therefore, it appears that Maier et al have produced an antibody that is identical to the claimed

antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibody with the antibody of Maier et al, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

h. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Summary

15. No Claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

Sheela Huff

SHEELA HUFF
PRIMARY EXAMINER